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Leading Article

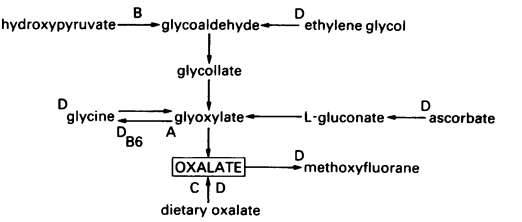
Treatment of enteric hyperoxaluria

Janice Harper and Martin A. Mansell

St Peter's Hospital and Institute of Urology, St Philip's Hospital, Sheffield Street, London WC2A 2EX, UK

Introduction

Calcium oxalate renal stones occur in about 10% of patients with a variety of gastrointestinal disorders characterized by malabsorption of bile salts, fatty acids or both.[1-4] Although hyperoxaluria is a common feature of all types of malabsorption, renal stones occur most frequently in those patients with extensive ileal resection, jejunoileal bypass (an operation performed for morbid obesity) or a previous history of urolithiasis. This review will briefly consider relevant aspects of oxalate metabolism and the pathogenesis of enteric hyperoxaluria (EHO) as a background to the possible treatment available for reducing hyperoxaluria and the risks associated with renal stone formation.



A. Primary hyperoxaluria Type I – alanine: glyoxylate aminotransferase deficiency; B. Primary hyperoxaluria Type II – D-glycerate dehydrogenase deficiency; C. Primary hyperoxaluria Type III – hyperabsorption of dietary oxalate in absence of bowl disease; D. Secondary hyperoxaluria (see Table I).

Figure 1 The main oxalate metabolic pathways in man and clinically important syndromes.

Oxalate metabolism

Oxalate is a dicarboxylic acid which has a number of useful functions in the plant kingdom but no obvious role in man. It is an end product of various metabolic pathways, summarized in Figure 1. Endogenous oxalate is derived principally from glyoxylate and ascorbic acid and was originally thought to contribute at least 90% of urinary oxalate, although recent studies in healthy subjects suggest that the contribution from the diet may be much greater.[5] Oxalate is excreted unchanged in the urine by a combination of glomerular filtration and tubular secretion and its clearance may be up to twice the glomerular filtration rate (GFR).[6]

Accurate measurement of plasma or urine oxalate has been hampered in the past by the presence of various substances which interfere with the assay, resulting in a gross overestimation of oxalate levels. An enzyme assay, based on the production of hydrogen peroxide using oxalate oxidase, has recently been described from this group of hospitals which avoids previous analytical problems and is applicable to both plasma[7] and urine.[8] The normal plasma oxalate concentration of 1-3 μmol/l obtained with this method agrees with indirect estimates based on isotope dilution techniques.[9] The normal range for 24 hour urine oxalate excretion is 0.1-0.45 mmol/24 h and the main causes of secondary hyperoxaluria are summarized in Table I. EHO is the commonest cause of secondary hyperoxaluria and is often associated with other risk factors for urinary stone formation such as oliguria, hypocitraturia, hypomagnesuria and hypophosphaturia. Patients with jejunoileal bypass form an important sub-group who have the lowest urinary volumes, greatest severity of hyperoxaluria, highest frequency of renal stones (up to 35%) and who may also be at risk of developing systemic oxalosis.[10,11]

Pathogenesis

There have been a number of mechanisms suggested to explain EHO. Hofmann's glyoxylate theory[12] proposed that bile salt glycine was converted to glyoxylate by colonic bacteria and that the absorbed glyoxylate was oxidized to oxalate in the liver. This theory must now be discarded because plasma glyoxylate levels, as reflected by normal urinary glycolate excretion, are not elevated in EHO[13] and radio-labelled glycine can-

Correspondence: M.A. Mansell, M.D., F.R.C.P.
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Table I Causes of secondary hyperoxaluria

1. Increased oxalate absorption	– Enteric hyperoxaluria
2. Increased endogenous oxalate synthesis	– Pyridoxine deficiency
3. Excess oxalate or precursor intake	– Oxalate
	Ascorbic acid
	Glycine
	Ethylene glycol
	Methoxyfluorane

not be detected as a major component of urinary oxalate.[14] More likely is the suggestion that hyperoxaluria results from enhanced gut oxalate absorption due either to increased oxalate solubility or increased colonic permeability. The solubility theory arose from studies which showed that patients with EHO absorbed up to 40% of dietary oxalate compared to about 10% in controls.[1,14–17] Additionally, urinary oxalate excretion falls after an oral dose of oxalate in these patients if oxalate and fat are restricted in their diets or calcium supplements are given. This is explained by a rise in the intraluminal concentration of calcium which precipitates oxalate from solution, making less available for absorption. However, not all the data can be explained simply in terms of oxalate solubility. The colon is the major site of oxalate absorption in EHO and it is known that colonic permeability to oxalate can be dramatically increased by the presence of unconjugated bile salts and long chain fatty acids, as occurs in patients with malabsorption.[18–20] The transport mechanism is likely to be the active chloride/bicarbonate system which has been characterized in the rabbit colon.[21]

Reduced anaerobic degradation of oxalate was implicated as a possible mechanism for hyperoxaluria when it was found that *Oxalobacter formigenes* was isolated less often in patients with steatorrhoea than in normal subjects.[22] It has subsequently been shown that while neomycin[17] and clindamycin[23] reduce bowel anaerobes in patients with EHO they do not affect the degree of hyperoxaluria, so that this mechanism is unlikely to be important.

Treatment

Specific treatment to reduce hyperoxaluria should be offered to those patients with EHO who are at greatest risk of developing renal stones. For the others, treatment of the underlying bowel disorder and maintaining a high fluid intake sufficient to achieve a urine output of 3 litres a day may be sufficient.

Dietary manipulation is a logical approach to reducing hyperoxaluria in view of its cause, although the low oxalate diets used in short-term studies are impossible to maintain on a long-term out-patient basis. More realistically the clinician should advise the patient to avoid oxalate-rich foods such as tea, coffee, cola-drinks, spinach, rhubarb, chocolate and peanuts. Additional benefit is gained by restricting the fat in the diet, supplemented, if necessary, by medium chain fatty acids. It should be noted that dietary advice, however well-meaning, is likely to fall on deaf ears in patients whose morbid obesity is of such severity that they have willingly submitted to the major surgery involved in a jejunoileal bypass.

Calcium supplementation, e.g. 2 g/day, precipitates oxalate in the gut and will reduce hyperoxaluria but it can also cause hypercalciuria.[24,25] Under these circumstances the saturation index for calcium oxalate in the urine may actually increase so it is essential that these urinary parameters are continually monitored.

Organic marine hydrocolloids (OMH) have recently been developed which bind oxalate to its calcium component. As this calcium is firmly bound to colloid it is unavailable for absorption, thereby reducing the risk of hypercalciuria.[26,27] In addition to a significant reduction in hyperoxaluria OMH also increases the inhibitory activity of urine to crystal formation. The mechanism remains to be elucidated but does not depend on a change in the urinary output of magnesium, citrate or phosphate. Initial reports[26] of long-term OMH therapy in small numbers of patients suggest that urinary stone recurrence rates may be reduced in a few individuals and larger trials are now in progress.

Cholestyramine can reduce urinary oxalate excretion to normal in patients with EHO by binding oxalate and bile salts, thereby exerting a dual influence via oxalate solubility and colonic permeability.[2,28,29] Long-term use is difficult because it may worsen the effects of steatorrhoea, resulting in malabsorption of folic acid and fat soluble vitamins.

Although allopurinol has been used successfully in patients with hyperuricaemia to reduce the risk

of recurrence of calcium oxalate stones[30] a recent trial shows it to be without effect on urinary oxalate excretion in patients with EHO.[31] Replenishing the natural inhibitors of crystal formation is a useful adjuvant to the specific measures outlined above[32] and can be achieved using a combination of magnesium, citrate and phosphate, e.g. magnesium glycerophosphate 1 g twice daily and potassium citrate 500 mg three times a day.

Recurrent renal stones which prove refractory to medical treatment may lead to impaired renal function with exacerbations caused by episodes of obstructive uropathy or pyelonephritis. Treatment of established calculi can often be satisfactorily achieved using a variety of non-invasive techniques such as extracorporeal shock-wave lithotripsy and percutaneous nephrolithotomy, averting the need for open surgery. The current consensus of opinion advises restorative bowel surgery only for patients with jejunoileal bypass who develop recurrent urolithiasis or progressive renal oxalosis.

Conclusion

All patients with EHO who have a jejunoileal bypass, extensive ileal resection or established renal stones should be offered specific treatment to reduce hyperoxaluria. This is caused by enhanced absorption of oxalate from the colon and can be corrected by dietary restriction of oxalate and fat combined with a high calcium intake, preferably as OMH. Patients should be monitored closely in order to detect the development of hypercalciuria, obstructive uropathy or progressive renal failure. It is still not clear why only a minority of patients with EHO develop renal stones and identification of the other factors involved could have major therapeutic implications.

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References

1. Dobbins, J.W. & Binder, H.J. Importance of the colon in enteric hyperoxaluria. *N Engl J Med* 1977, **296:** 298–301.
2. Smith, L.H., Fromm, H. & Hofmann, A.F. Acquired hyperoxaluria, nephrolithiasis and intestinal disease. Description of a syndrome. *N Engl J Med* 1972, **286:** 1371–1375.
3. Dowling, R.H., Rose, G.A. & Suter, D.J. Hyperoxaluria and renal calculi in ileal disease. *Lancet* 1971, **i:** 1103–1106.
4. O'Leary, P., Thomas, P.W. & Woodward, E.R. Urinary tract stone after small bowel bypass for morbid obesity. *Am J Surg* 1973, **127:** 142–147.
5. Rose, G.A. Introduction. In: Rose, G.A. (ed.) *Oxalate Metabolism in Relation to Urinary Stone*. Springer-Verlag, Berlin, Heidelberg, 1988, pp. 1–6.
6. Constable, A.R., Joekes, A.M., Kasidas, G.P., O'Regan, P. & Rose, G.A. Plasma level and renal clearance of oxalate in normal subjects and in patients with primary hyperoxaluria or chronic renal failure or both. *Clin Sci* 1979, **56:** 299–304.
7. Kasidas, G.P. Assay of oxalate in plasma. In: Rose, G.A. (ed.) *Oxalate Metabolism in Relation to Urinary Stone*. Springer-Verlag, Berlin, Heidelberg, 1988, pp. 45–64.
8. Kasidas, G.P. Assay of oxalate and glycollate in urine. In: Rose, G.A. (ed.) *Oxalate Metbolism in Relation to Urinary Stone*. Springer-Verlag, Berlin, Heidelberg, 1988, pp. 7–26.
9. Williams, H.E., Johnson, G.A. & Smith, L.H. The renal clearance of oxalate in normal subjects and in patients with primary hyperoxaluria. *Clin Sci* 1971, **41:** 213–218.
10. Morgan, S.H., Watts, R.W.E., Purkiss, P., Mansell, M.A., Rose, G.A. & Pilkington, T.R.E. Jejunoileal bypass, hyperoxaluria and systemic oxalosis. *Clin Sci* 1986, **15** (Suppl): 34p.
11. Watts, R.W.E., Veall, N. & Purkiss, P. Sequential studies of oxalate dynamics in primary hyperoxaluria. *Clin Sci* 1983, **65:** 627–633.
12. Hofmann, A.F., Thomas, P.J., Smith, L.H. *et al.* Pathogenesis of secondary hyperoxaluria in patients with ileal resection and diarrhoea. *Gastroenterology* 1970, **58:** 960.
13. Admirand, W.H., Earnest, D.L. & Williams, H.E. Hyperoxaluria and bowel disease. *Trans Assoc Am Physicians* 1971, **84:** 307–312.
14. Chadwick, V.S., Modha, K. & Dowling, R.H. Mechanism for hyperoxaluria in patients with ileal dysfunction. *N Engl J Med* 1973, **289:** 172–176.
15. Earnest, D.L., Johnson, G., Williams, H.E. & Admirand, W.H. Hyperoxaluria in patients with ileal resection: an abnormality in dietary oxalate absorption. *Gastroenterology* 1973, **66:** 1114–1122.
16. Andersson, H. & Jagenburg, R. Fat-reduced diet in the treatment of hyperoxaluria in patients with ileopathy. *Gut* 1974, **15:** 360–366.
17. Hofman, A.K., Laker, M.F., Dharmsathaphorn, K., Sherr, H.P. & Lorenzo, D. Complex pathogenesis of hyperoxaluria after jejunoileal bypass surgery. Oxalogenic substances in diet contribute to urinary oxalate. *Gastroenterology* 1983, **84:** 293–300.
18. Chadwick, V.S., Elias, E., Bell, G.D. & Dowling, R.H. The role of bile acids in the increased intestinal absorption of oxalate after ileal resection. In: Matern, S., Hackenschmidt, J., Back, P. & Gerok, W. (eds) *Advances in Bile Acid Research*. Schattauer, Stuttgart, 1975, pp. 435–438.
19. Dobbins, J.W. & Binder, H.J. Effect of bile salts and fatty acids on the colonic absorption of oxalate. *Gastroenterology* 1976, **70:** 1096–1100.
20. Fairclough, P.D., Feest, T.G., Chadwick, V.S. & Clark, M.L. Effect of sodium chenodeoxycholate on oxalate absorption from the excluded human colon – a mechanism for 'enteric' hyperoxaluria. *Gut* 1977, **18:** 240–244.
21. Hatch, M., Freel, R.W., Goldner, A.M. & Earnest, D.L. Oxalate and chloride absorption by the rabbit colon: sensitivity to metabolic and anion transport inhibitors. *Gut* 1984, **25:** 232–237.
22. Goldkind, R., Cave, D.R., Jaffin, B., Bliss, C.M. & Allison, M.J. Bacterial oxalate metabolism in the human colon: a possible factor in enteric hyperoxaluria. *Gastroenterology* 1986, **90:** 1431.
23. Nordenvall, K.T., Hallberg, D., Larsson, L. & Nord, C.E. The effect of clindamycin on the intestinal flora in patients with enteric hyperoxaluria. *Scand J Gastroenterol* 1983, **18:** 177–181.
24. Barilla, D.E., Notz, C., Kennedy, D. & Pak, C.Y.C. Oxalate absorption and excretion. *Am J Med* 1978, **64:** 579–585.
25. Hylander, E., Jarnum, S. & Nelsen, K. Calcium treatment of enteric hyperoxaluria after JIB for morbid obesity. *Scand J Gastroenterol* 1980, **15:** 349–352.

26. Lindsjö, M., Fellström, B., Ljunghall, S., Wikström, B. & Danielson, B.G. Treatment of enteric hyperoxaluria with calcium-containing organic marine hydrocolloid. *Lancet* 1989, **ii:** 701–704.
27. Lindsjö, M. Oxalate metabolism in renal stone disease with special reference to calcium metabolism and intestinal absorption. *Scand J Urol Nephrol* 1989, **24:** 1–53.
28. Binder, H.J. Intestinal oxalate absorption. *Gastroenterology* 1974, **67:** 441–446.
29. Stauffer, J.O., Humphreys, M.H. & Weir, G.J. Acquired hyperoxaluria with regional enteritis after ileal resection: role of dietary oxalate. *Ann Intern Med* 1973, **79:** 383–391.
30. Ettinger, B., Tang, A., Citron, J.T., Livermore, B. & Williams, T. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986, **315:** 1386–1389.
31. D'Cruz, D.P., Rampton, D.S. & Rose, G.A. Failure of allopurinol to modify urinary composition in enteric hyperoxaluria. *Br J Urol* 1989, **64:** 231–234.
32. Rudman, D., Dedonis, J.L., Fountain, M.T. *et al.* Hypocituria in patients with gastrointestinal malabsorption. *N Engl J Med* 1980, **303:** 657–661.